Using Serum Creatinine To Estimate Glomerular Filtration Rate: Accuracy in Good Health and in Chronic Kidney Disease

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Background: **The National Kidney Foundation has advocated the use of the abbreviated Modification of Diet in Renal Disease (MDRD) equation to estimate glomerular filtration rate (GFR) from serum creatinine measurements in clinical laboratories. However, healthy persons were not included in the development of the MDRD equation.**

Objectives: **To assess the accuracy of the MDRD equation in patients with chronic kidney disease compared with healthy persons and to develop a new equation that uses both patients with chronic kidney disease and healthy persons.**

Design: **Cross-sectional study.**

Setting: **The Mayo Clinic, a tertiary-care medical center.**

Participants: **Consecutive patients ($n = 320$) who had an iothalamate clearance test specifically for chronic kidney disease evaluation and consecutive healthy persons ($n = 580$) who had an iothalamate clearance test specifically for kidney donor evaluation.**

Measurements: **Serum creatinine levels, GFR, demographic characteristics, and clinical characteristics were abstracted from the medical record.**

Results: **The MDRD equation underestimated GFR by 6.2% in patients with chronic kidney disease and by 29% in healthy persons. Re-estimated coefficients for serum creatinine and sex were similar to the original MDRD equation in the chronic kidney disease series but not in the healthy series. At the same serum creatinine level, age, and sex, GFR was on average 26% higher in healthy persons than in patients with chronic kidney disease ($P < 0.001$). A quadratic GFR equation was developed to estimate logarithmic GFR from the following covariates: 1/SCr, $1/SCr^2$, age, and sex (where SCr = serum creatinine).**

Limitations: **The new equation was not developed in a general population sample. Elderly and African-American persons were underrepresented.**

Conclusion: **The MDRD equation systematically underestimates GFR in healthy persons. A new equation developed with patients who have chronic kidney disease and healthy persons may be a step toward accurately estimating GFR when the diagnosis of chronic kidney disease is unknown.**

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See editorial comment on pp 959-961.

Recently, the National Kidney Foundation endorsed a series of guidelines to assess patients with chronic kidney disease. These guidelines highlighted problems associated with using creatinine clearance to measure glomerular filtration rate (GFR). They instead recommended estimation of GFR by using prediction equations based on serum creatinine determinations (1, 2). The abbreviated Modification of Diet in Renal Disease (MDRD) equation (3, 4) was advocated because it correlated well with GFR measured by iothalamate clearance (2, 5). It also performed as well as a more complicated MDRD equation that required serum urea nitrogen and albumin determinations (3).

The abbreviated MDRD equation has also been used to estimate the prevalence of chronic kidney disease in the U.S. population with serum creatinine determinations adjusted for calibration bias (6, 7). However, this equation was developed by using persons with chronic kidney disease and did not include healthy persons (3, 4). Thus, the MDRD equation may not be appropriate for determining the prevalence of chronic kidney disease. Previous studies have raised the concern that MDRD equations may underestimate GFR in healthier populations (8–12). Furthermore, in a population-based study, the relationship between cardiovascular risk factors and GFR differed when the abbreviated MDRD equation was used instead of creatinine clearance (13).

The primary objective of the current study was to determine whether estimated GFR with the MDRD equation was accurate in healthy persons compared to patients with chronic kidney disease. The secondary objective was to develop a new GFR prediction equation based on both healthy persons and patients with chronic kidney disease.

METHODS

Healthy and Chronic Kidney Disease Series

Records of all potential living donors for kidney transplantation at the Mayo Clinic from 1996 to 2002 were reviewed, with institutional review board approval; this review was an expansion of a previously reported series (9). Originally, potential kidney recipients had identified the potential donors and had perceived them to be healthy enough to be evaluated for kidney donation. Most donors (71%) were related to the potential kidney recipient (9). A total of 599 potential donors had an iothalamate clearance test to measure GFR, which was routinely obtained before a clinic visit with a nephrologist (**Figure 1**). After exclusions for missing serum creatinine determinations or for age younger than 17 years, the healthy series consisted of 580 potential donors.

Records of 501 consecutive patients who had an iothalamate clearance test for any reason between October 1999 and March 2000 were also reviewed, with institutional review board approval (**Figure 1**). A nephrologist

Context

Experts increasingly use the Modification of Diet in Renal Disease (MDRD) equation to estimate glomerular filtration rate (GFR).

Contribution

This cross-sectional study compared GFR estimated by the MDRD equation with GFR measured by iothalamate clearance in 320 patients with chronic kidney disease and 580 healthy kidney donor candidates. The MDRD equation underestimated GFR by 6% in patients with kidney disease and by 29% in healthy persons. The authors also derived a quadratic equation that better estimated GFR in the healthy people than did the MDRD equation.

Implications

The MDRD equation systematically underestimates GFR and may erroneously categorize some healthy persons as having kidney disease.

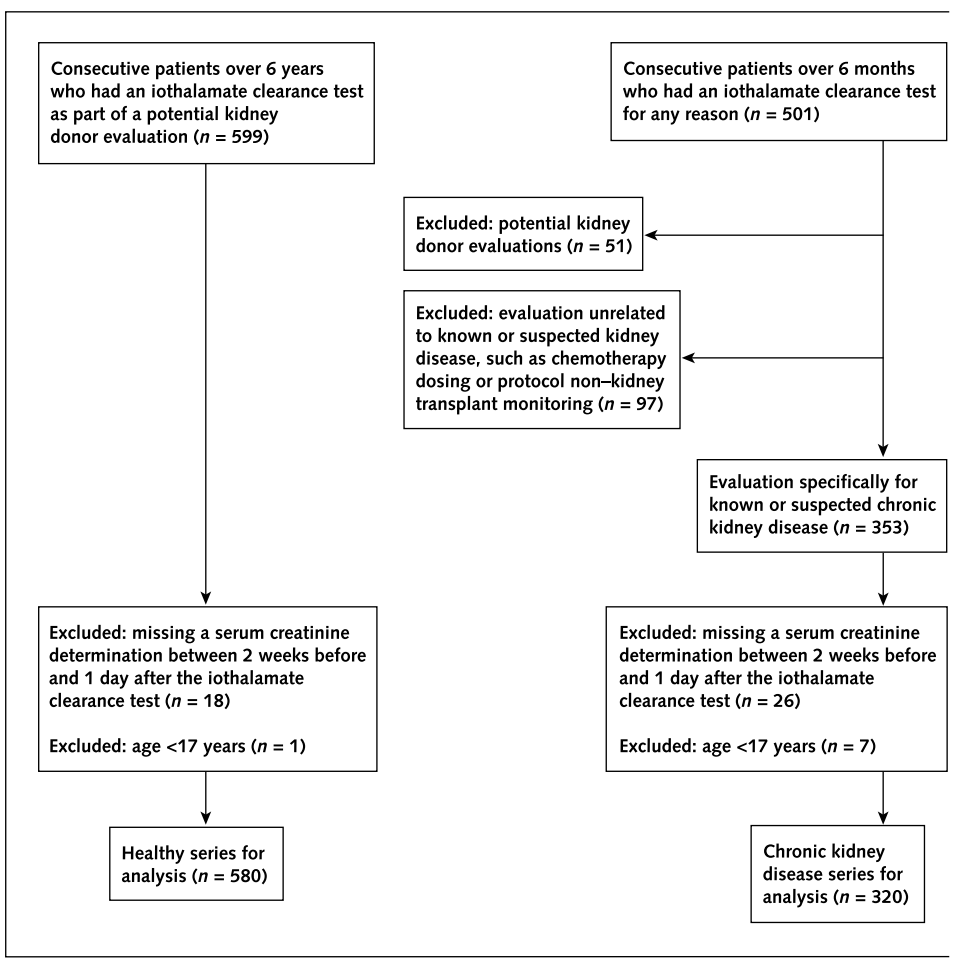
–The Editors

abstracted these records for a cystatin C study (14). Of these patients, 353 had an iothalamate clearance test to measure GFR as part of an evaluation for known or suspected chronic kidney disease. Iothalamate clearance was routinely and primarily ordered by nephrologists at the Mayo Clinic during outpatient referrals. An elevated serum creatinine level, proteinuria, abnormal urinary sediment, history of kidney disease, or kidney transplantation recipient status were typical indications for the iothalamate clearance test. Thus, chronic kidney disease was defined by clinical presentation and not by a GFR cutoff. In recipients of a nonkidney solid organ transplant, iothalamate clearance for routine monitoring only was not considered an evaluation for chronic kidney disease. After exclusions for missing serum creatinine determinations or for age younger than 17 years, the chronic kidney disease series consisted of 320 patients.

Iothalamate Clearance and Serum Creatinine Assays

Measurement of GFR with the renal clearance of nonradiolabeled iothalamate has previously been described (15). This test involved the subcutaneous injection of nonradiolabeled iothalamate after oral hydration with 4 to 6 glasses of water. After 2 hours, GFR was determined by the

Figure 1. **Sampling process for healthy series and chronic kidney disease series.**



clearance equation (UV/P) using the average of 2 serum samples and 1 urine sample assayed for iothalamate concentration via capillary electrophoresis. Glomerular filtration rate was expressed per 1.73 m^2 by multiplying the measured value by 1.73 and dividing by body surface area. Nonradiolabeled iothalamate clearance correlates well with radiolabeled iothalamate clearance ($r = 0.998$) (15) and provides a normal value range similar to that of other GFR measurement techniques (9, 16). Interassay coefficient of variation for nonradiolabeled iothalamate clearance was reported as 5%.

Serum creatinine levels were all assayed with the rate-Jaffe reaction on a Hitachi 747 autoanalyzer (Roche Diagnostics Corp., Indianapolis, Indiana). This assay was calibrated daily with a Cfas calibrator (Roche Diagnostics Corp.) by using the uncompensated method during the study period. The interassay coefficient of variation for serum creatinine determinations was reported as 3.1% at 1.3 mg/dL (115 μmol/L) and 1.5% at 6.1 mg/dL (539 μmol/L) with stability during the study period. The 2.5th to 97.5th percentile of serum creatinine by this assay was 0.7 to 1.2 mg/dL (62 to 106 μmol/L) in normal white women and 0.9 to 1.4 mg/dL (80 to 124 μmol/L) in normal white men. Estimated GFR was calculated by using the abbreviated MDRD equation (**Table 1**, equation 1).

Table 1. **Prediction Equations for Glomerular Filtration Rate***

Equation 1: Original MDRD equation (1628 patients with chronic kidney disease) (4)

$$GFR = 186 \times SCr^{-1.154} \times Age^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}$$

Equation 2: Refit MDRD equation (320 predominantly white patients with chronic kidney disease)

$$GFR = 297 \times SCr^{-1.290} \times Age^{-0.290} \times 0.767 \text{ (if female)}$$

Equation 3: Refit MDRD equation (580 predominantly white healthy persons)

$$GFR = 216 \times SCr^{-0.490} \times Age^{-0.192} \times 0.923 \text{ (if female)}$$

Equation 4: Refit MDRD equation with healthy indicator variable (320 patients with chronic kidney disease and 580 healthy persons)

$$GFR = 224 \times SCr^{-1.190} \times Age^{-0.236} \times 0.796 \text{ (if female)} \times 1.26 \text{ (if healthy)}$$

Equation 5: Quadratic GFR equation (320 patients with chronic kidney disease and 580 healthy persons)

$$GFR = \exp\left(1.911 + \frac{5.249}{SCr} - \frac{2.114}{SCr^2} - 0.00686 \times Age - 0.205 \text{ (if female)}\right)$$

If SCr < 0.8 mg/dL, use 0.8 for SCr

* GFR = glomerular filtration rate (mL/min per 1.73 m^2); MDRD = Modification of Diet in Renal Disease; SCr = serum creatinine (mg/dL). Age is in years. Numbers in parentheses are the population used to derive the equation.

Statistical Analysis

We compared the baseline characteristics of patients in the healthy and chronic kidney disease series by using the chi-square test (nominal factors), Wilcoxon rank-sum, or Student *t*-test. We defined bias as the mean of estimated GFR minus measured GFR. We defined percentage bias as the mean of individual ([estimated GFR − measured GFR]/measured GFR) × 100%. P30% was defined as the percentage of estimated GFR within 30% of measured GFR. We compared estimated GFR and measured GFR in the healthy and chronic kidney disease series by using bias, percentage bias, R^2 (coefficient of determination), and P30%. Similar analyses were done with the Cockcroft–Gault equation (17), adjusted for body surface area (mL/min per 1.73 m^2) and adjusted to predict GFR instead of creatinine clearance (3).

The log-linear form of the abbreviated MDRD equation was refit for new coefficients by using multiple linear regression in the healthy and chronic kidney disease series independently. A log-linear form of the abbreviated MDRD equation was also refit in a combined series ($n = 900$) with an indicator variable for healthy versus kidney disease status. Each coefficient was compared with the original MDRD study coefficient (4).

To develop a new equation for use when the diagnosis of chronic kidney disease is unknown, we used an approach similar to that used to develop the MDRD equations (3, 4). The natural logarithmic (ln) transformed measured GFR was regressed on age, sex, and serum creatinine in the combined series. Because the relationship of ln GFR with ln serum creatinine was nonlinear, the following terms were considered: linear, quadratic, and cubic reciprocal serum creatinine. Linear, quadratic, and logarithmic age terms were also considered. In addition, we examined pairwise interactions between the 3 factors. Because of the large sample size, terms that were statistically significant often added little to the predictive ability of the model. In the interest of parsimony, an increase in R^2 of 0.02 or more was arbitrarily required to consider a more complicated model (18). The new equation was internally validated by using bootstrapping (500 replications) to estimate its performance (R^2 adjusted for optimism) on independent data sets (19).

All statistical analyses were performed with JMP, version 5.1 (SAS Institute, Inc., Cary, North Carolina), except for bootstrapping, which was done with SAS, version 8.2.

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RESULTS

Comparison of Healthy and Chronic Kidney Disease Series

Table 2 shows the characteristics of the patient samples. Information on race was not available in 14% of the patients. The number of African-American patients was inadequate to analyze the race component in either series. In the chronic kidney disease series, 53% of patients had

Table 2. **Clinical Characteristics in the Healthy Series and Chronic Kidney Disease Series***

Characteristic	Healthy ($n = 580$)	Chronic Kidney Disease ($n = 320$)
Mean age ± SD (range), *y*	41 ± 11 (18–72)	53 ± 15 (17–87)
Female, *n (%)*	334 (58)	126 (39)
African American, *n (%)*†	7 (1.2)	0 (0.0)
Mean height ± SD (range), *cm*	171 ± 9.3 (147–198)	171 ± 9.8 (137–195)
Mean weight ± SD (range), *kg*	82 ± 18 (47–162)	84 ± 21 (37–193)
Mean body mass index ± SD (range), kg/m^2	27.8 ± 5.3 (16.7–59.0)	28.8 ± 6.2 (14.2–64.7)
Mean serum creatinine level ± SD (range), *mg/dL*	1.05 ± 0.16 (0.6–1.6)	1.93 ± 0.97 (0.7–8.8)
Mean measured GFR, *mL/min per 1.73 m²*	101 ± 17 (63–177)	48 ± 25 (5–133)
Measured GFR and serum creatinine level obtained the same day, *n (%)*	517 (89)	203 (63.4)

* Race information was not available in 14% of the patients. GFR = glomerular filtration rate.
† $P < 0.05$ with the chi-square test, Wilcoxon rank-sum test, or Student *t*-test, where appropriate.

native kidney disease alone, 16% of patients had a non-kidney solid organ transplant with or without a kidney transplant, and 31% of patients had a kidney transplant alone. In the patients with native kidney disease alone, 36% had hypertension or kidney disease of unknown cause, 24% had glomerulopathy, 13% had diabetes mellitus, and the remaining 27% had miscellaneous causes. Serum creatinine levels were normal (≤1.4 mg/dL [≤124 μmol/L] in men and ≤1.2 mg/dL [≤106 μmol/L] in women) in 93 (29%) of the chronic kidney disease series.

Figure 2 displays estimated GFR (abbreviated MDRD equation) plotted against measured GFR (iothalamate clearance). Estimated GFR predicted measured GFR well in the chronic kidney disease series, but measured GFR was higher than estimated GFR in the healthy series. **Table 3** shows the accuracy and precision of estimated GFR calculated by using the original MDRD equation. The MDRD equation was less accurate in the healthy series than in the chronic kidney disease series. With the Cockcroft–Gault equation, percentage bias was −5.9% ± 1.7% in the chronic kidney disease series, −9.6% ± 3.9% in the chronic kidney disease series with an estimated GFR of 60 mL/min per 1.73 m^2 or greater ($n = 61$), and −27% ± 1% in the healthy series. Thus, the Cockcroft–Gault equation was also less accurate in the healthy series than in the chronic kidney disease series.

The top panel of **Figure 3** displays the reciprocal of serum creatinine plotted against logarithmic measured GFR. At any serum creatinine level, patients in the healthy series had a higher average GFR than did patients in the chronic kidney disease series. Patients with chronic kidney disease who had transplants were similar to patients with chronic kidney disease who did not have transplants.

The refit MDRD equations derived in this study were compared with the original MDRD equation (equation 1). In the chronic kidney disease series (equation 2), the coefficients (±SE) were similar to the original MDRD equation for serum creatinine (−1.290 ± 0.039 vs. −1.154), age (−0.290 ± 0.050 vs. 0.203), and female sex (0.767 [exp(−0.265 ± −0.032)] vs. 0.742 [exp(−0.298)]). Adding a transplant status variable was not statistically significant ($P > 0.2$) and did not change the serum creatinine, age, or sex coefficients substantively. In the healthy series (equation 3), the age coefficient was also similar to the original MDRD equation (−0.192 ± 0.021 vs. 0.203). However, the coefficients were very different from the original MDRD equation for serum creatinine (−0.490 ± 0.052 vs. −1.154) and for female sex (0.923 [exp(−0.080 ± 0.016)] vs. 0.742 [exp(−0.298)]). At the same serum creatinine level, women had 77% the GFR of men in the chronic kidney disease series but 92% the GFR of men in the healthy series.

When health status was added as a separate variable in a refit MDRD equation (equation 4), healthy persons had a 26% higher GFR on average than did patients with chronic kidney disease ($P < 0.001$). However, health status was better modeled as an effect modifier on the relationship between serum creatinine and GFR. For example, a 60-year-old man with a serum creatinine level of 1.4 mg/dL (124 μmol/L) (high-normal) would have a 42% higher GFR (83 vs. 59 mL/min per 1.73 m^2) if he was healthy (equation 3) than if he had chronic kidney disease (equation 2). But a 60-year-old man with a serum creatinine level of 0.9 mg/dL (80 μmol/L) (low-normal) would have the same GFR (104 mL/min per 1.73 m^2) whether he was healthy or had chronic kidney disease. Likewise, a 60-year-old woman with a serum creatinine level of 1.2 mg/dL (106 μmol/L) (high-normal) would have a 51% higher GFR (83 vs. 55 mL/min per 1.73 m^2) if she was healthy than if she had chronic kidney disease. But a 60-year-old woman with a serum creatinine level of 0.7 mg/dL (62 μmol/L) (low-normal) had nearly the same GFR (108 vs. 110 mL/min per 1.73 m^2) whether she was healthy or had chronic kidney disease.

Development and Validation of a New Equation

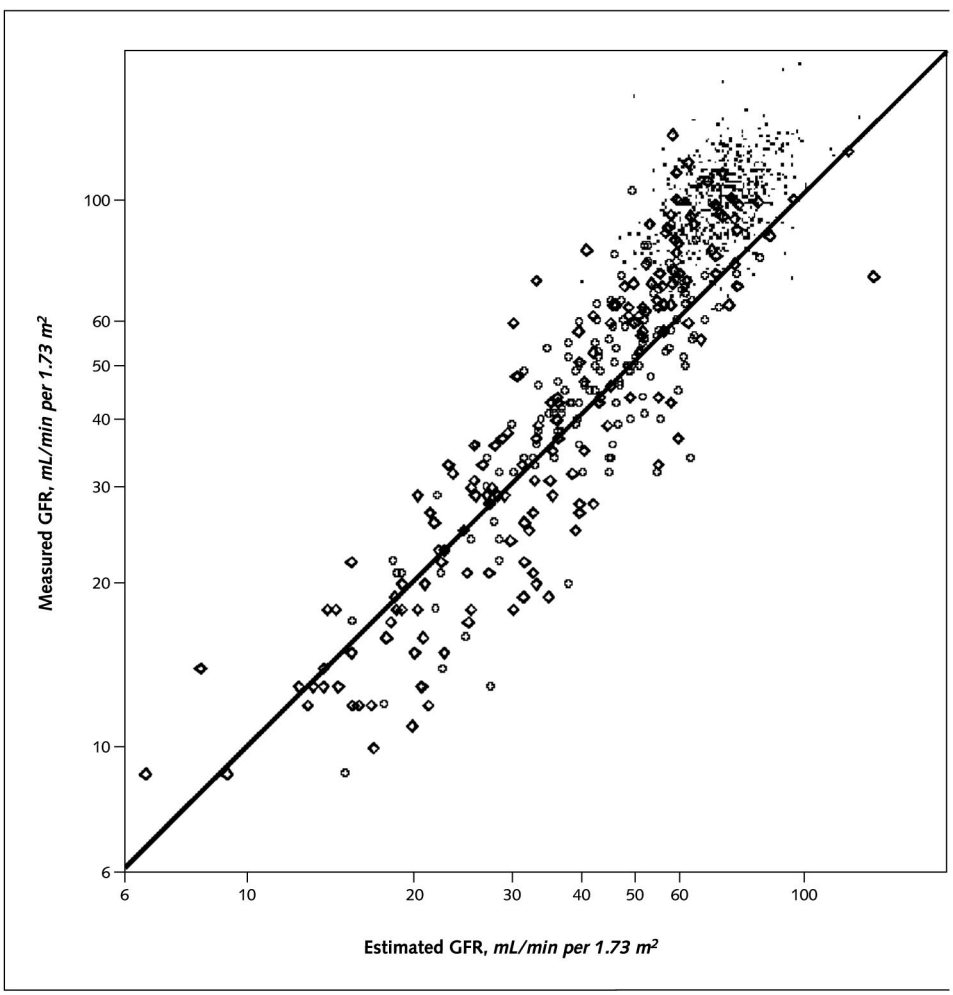
In clinical practice, it may be unknown whether a patient is healthy or has chronic kidney disease. Thus, a new equation was developed on the basis of a combined sample of healthy persons and patients with chronic kidney disease. The best model was the quadratic GFR equation with the following covariates: 1/SCr, $1/SCr^2$, age, and sex

(where SCr = serum creatinine) to predict ln measured GFR (equation 5). Serum creatinine values less than 0.8 mg/dL (71 μmol/L) were set to 0.8 in the development of this equation. Inclusion of all pairwise interactions increased the R^2 value by only 0.007. The quadratic GFR equation (R^2 = 0.863, equation 5) fit the combined series better than the original MDRD equation (R^2 = 0.830, equation 1) and a refit MDRD equation derived by using the combined series (R^2 = 0.841, equation not shown). The bootstrap corrected R^2 for the quadratic model was 0.862 compared with 0.863 uncorrected. The bottom panel of **Figure 3** compares the quadratic GFR equation with the original MDRD equation. The quadratic GFR equation had a higher estimated GFR in the normal serum creatinine range.

DISCUSSION

These analyses indicate that although the abbreviated MDRD equation was reasonably accurate in patients with chronic kidney disease, it significantly underestimated GFR in healthy persons. This was probably due to the exclusion of healthy persons from the study participants used to develop this equation. At the same serum creatinine level, age, and sex, GFR was on average 26% higher in healthy persons than in patients with chronic kidney disease. A new quadratic GFR equation may be more accurate than the MDRD equation in estimating GFR when kidney disease status is unknown. This study highlights the importance of selection bias in the target population used to develop GFR prediction equations. Thus, the application of the MDRD equation to the general population (7)

Figure 2. **Relationship between estimated glomerular filtration rate (*GFR*) (abbreviated Modification of Diet in Renal Disease equation) and measured GFR (iothalamate clearance) in 900 patients on a logarithmic scale.**



Diamonds represent the patients with chronic kidney disease without transplants (n = 168). Circles represent patients with chronic kidney disease with transplants (n = 152). Dots represent the healthy series (n = 580). The solid line is identity. The healthy series has a higher measured GFR than estimated GFR.

may have overestimated the prevalence of chronic kidney disease (when defined by a reduced GFR).

A concern with GFR prediction equations has been bias from a lack of standard calibration in serum creatinine assays across laboratories (20). One study found that the MDRD study laboratory had serum creatinine values 0.23 mg/dL (20 μmol/L) lower than values measured at another laboratory. The implication was that a constant calibration bias caused greater inaccuracies in estimated GFR for persons with a normal serum creatinine level than for persons with an elevated serum creatinine level (6). Calibration bias is being addressed by the Laboratory Working Group of the National Kidney Disease Education Program (21). Correction of this calibration bias, however, does not rectify a selection bias present in the original MDRD equation. After subtracting 0.23 mg/dL (20 μmol/L) from all serum creatinine values (6), GFR (with multivariable adjustment [serum creatinine level, age, and sex]) was still 26% higher in healthy persons than in patients with chronic kidney disease.

To further investigate the potential effect of calibration, serum samples assayed for creatinine ($n = 180$) were reassayed at Loyola University Medical Center on a rate-Jaffe Beckman LX20 autoanalyzer (Beckman Coulter, Inc., Fullerton, California). A rate-Jaffe Beckman CX3 autoanalyzer (older model) was used for deriving the original MDRD equation (6). A calibration equation ($SCr_{Loyola} = -0.18 + 1.14 \times SCr_{Mayo}$) was derived to adjust the serum creatinine values. This adjustment slightly improved bias with the MDRD equation in the healthy series (−29% before calibration, −26% after calibration) but led to more bias in the chronic kidney disease series (−6.2% before calibration, −9.5% after calibration). However, GFR (with multivariable adjustment) was still 26% higher in healthy persons than in patients with chronic kidney disease.

The additive effects of calibration bias and selection bias may explain why 12% of the middle-aged healthy series had an estimated GFR less than 60 mL/min per 1.73 m^2 with the MDRD equation, diagnostic criteria for chronic kidney disease (2). For example, if a 50-year-old woman presented to donate a kidney and had a Mayo Clinic serum creatinine level of 1.1 mg/dL (97 μmol/L), she would have an estimated GFR of 90 mL/min per 1.73 m^2 (equation 3). If instead an equation derived with the Mayo Clinic chronic kidney disease sample were used (equation 2), her estimated GFR would be 65 mL/min per 1.73 m^2. But if an equation derived with the MDRD study chronic kidney disease sample were used (equation 1), her estimated GFR would be 56 mL/min per 1.73 m^2.

One possible explanation for a selection bias in the MDRD equation is that healthy persons may have more muscle mass and more protein intake than patients with chronic kidney disease who are chronically ill and have protein-restricted diets. Substantial muscle atrophy has been shown to occur in patients receiving dialysis compared with healthy controls (22). In patients who develop kidney disease, the increase in serum creatinine level caused by GFR reduction may be attenuated by muscle atrophy and decreased dietary protein. A decrease in serum creatinine level was evident in a comparison of a healthy person to a patient with kidney disease who had the same GFR, age, and sex. For example, consider a 60-year-old man with a GFR of 83 mL/min per 1.73 m^2. If healthy, a serum creatinine level of 1.4 mg/dL (124 μmol/L) would be required to estimate this GFR (equation 3). But if he had kidney disease, a lower serum creatinine level of 1.07 mg/dL (95 μmol/L) would be required to estimate this GFR (equation 2).

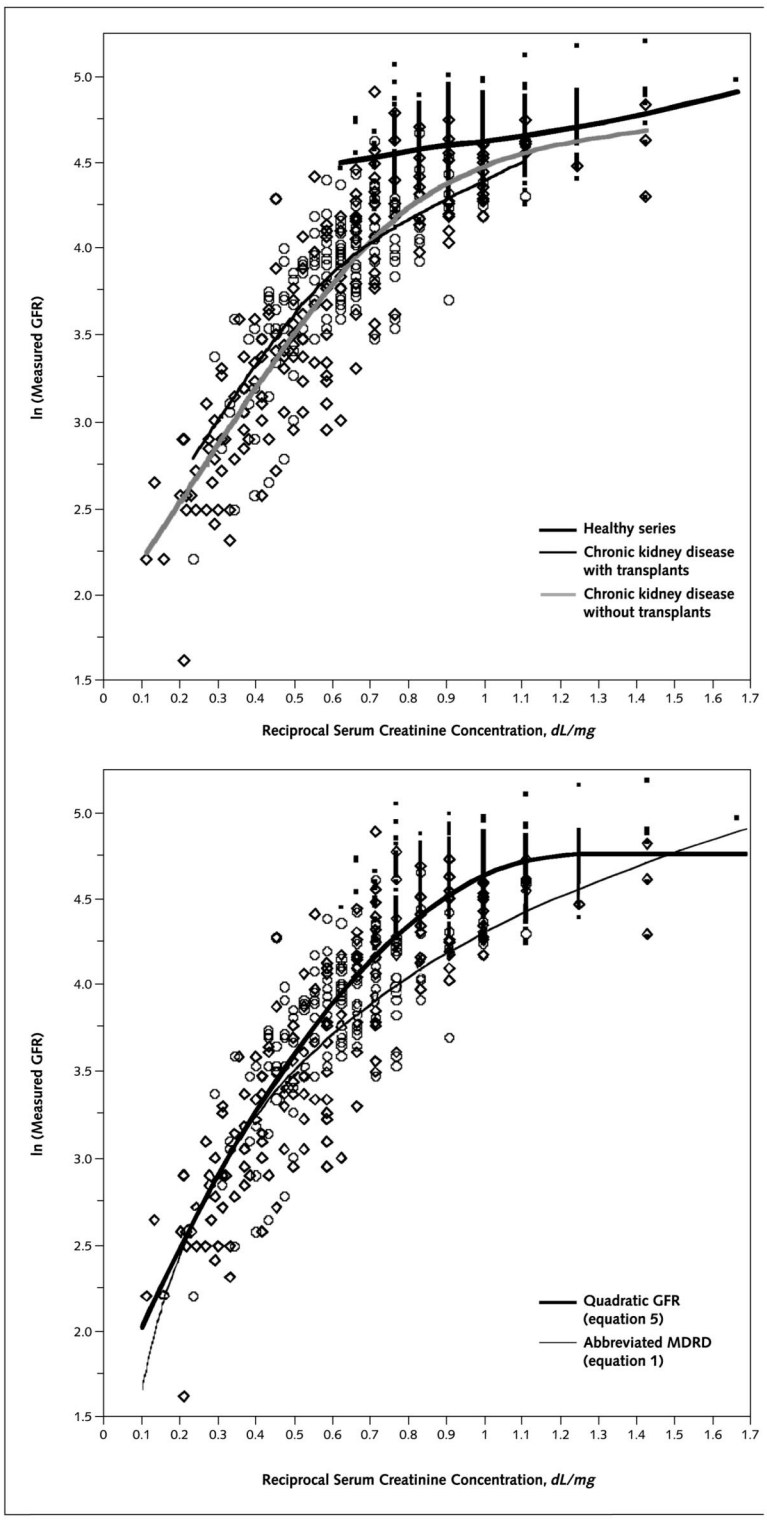
The physiology for serum creatinine variability may also differ in patients with chronic kidney disease compared with healthy persons. Consistent with this hypothesis, the serum creatinine coefficients calculated in kidney disease samples for this study (−1.290) and the MDRD study (−1.154) (4) were much stronger than those calculated in healthy samples for this study (−0.490) and by

Table 3. **Accuracy and Precision of the Abbreviated Modification of Diet in Renal Disease Equation in the Chronic Kidney Disease Series and Healthy Series***

Variable	Chronic Kidney Disease Series	Chronic Kidney Disease Series Subset (Patients with Estimated GFR† ≥ 60 mL/min per 1.73 m^2)	Healthy Series
Sample size	320	49	580
Measured GFR, *mL/min per 1.73 m^2*†	48 ± 25 (5–133)	80 ± 20 (34–124)	101 ± 17 (63–177)
Estimated GFR, *mL/min per 1.73 m^2*‡	43 ± 18 (6–134)	72 ± 14 (60–134)	72 ± 11 (40–127)
Bias ± SE, *mL/min per 1.73 m^2*§	−5.5 ± 0.8	−8.1 ± 2.8	−29 ± 1
Percentage bias ± SE, %‖	−6.2 ± 1.6	−8.5 ± 3.7	−29 ± 1
P30%¶	75	84	54
R^2 (logarithmic)	0.786	0.152	0.186

* GFR = glomerular filtration rate.
† Measured GFR by iothalamate clearance given as mean ± SD (range).
‡ Estimated GFR by abbreviated Modification of Diet in Renal Disease equation given as mean ± SD (range).
§ Bias was mean (estimated GFR − measured GFR).
‖ Percentage bias was mean individual ([estimated GFR − measured GFR]/measured GFR) × 100%.
¶ P30% was percentage of estimated GFR within 30% of measured GFR.

Figure 3. **Relationship between the reciprocal of serum creatinine and the natural logarithm of measured glomerular filtration rate (*GFR*) in 900 patients.**



Diamonds represent the patients with chronic kidney disease without transplants (n = 168). Circles represent patients with chronic kidney disease with transplants (n = 152). Dots represent the healthy series (n = 580). **Top.** Smoothed curve fits (JMP 5.01; λ = 0.1) applied to data. Note that the healthy series is higher across all serum creatinine levels. **Bottom.** GFR prediction equations using the mean age (46 years) and female frequency (49%) of the combined series. Note that the quadratic GFR equation better fits the data. MDRD = Modification of Diet in Renal Disease.

other investigators (−0.113) (8). The difference in coefficients may be explained through the relationship between serum creatinine and GFR as expressed in the following clearance equation: $S_{Cr} = U_{Cr}V/GFR$. In healthy persons, muscle mass and dietary protein intake ($U_{Cr}V$) (23, 24) may have the dominant effect on serum creatinine variability, consistent with a weak coefficient in predicting GFR. For example, a 50% higher serum creatinine level in the healthy series was associated with an 18% lower GFR. In patients with kidney disease, GFR may have the dominant effect on serum creatinine variability, consistent with a strong coefficient in predicting GFR. For example, a 50% higher serum creatinine level in the chronic kidney disease series was associated with a 41% lower GFR. This was stronger than an inverse association, possibly reflecting the increasing role of tubular secretion as GFR declines (23).

The quadratic GFR equation (equation 5) was developed by using a combined healthy and chronic kidney disease sample as a step toward improving the estimation of GFR when kidney disease status is unknown. Only 1 person (0.2%) in the healthy series had an estimated GFR less than 60 mL/min per 1.73 m^2 with the quadratic GFR equation. However, this equation has several limitations. The quadratic GFR equation assumes that persons with a normal serum creatinine level can be represented by a population in which 14% of patients had chronic kidney disease and 86% were potential kidney donors. The potential kidney donors may be "super healthy" compared with the general population. However, they were not without comorbid conditions: 29% had a high blood pressure (systolic ≥ 140 mm Hg or diastolic ≥ 90 mm Hg) and 33% had hyperlipidemia (low-density lipoprotein cholesterol level > 130 mg/dL [>3.4 mmol/L]). A GFR prediction equation developed in a population-based sample would be more accurate for general population studies. Also, the sample used to derive the quadratic GFR equation lacks adequate representation of elderly patients and nonwhite racial groups.

Several additional limitations in this study should be noted. Serum creatinine and GFR determinations were not always assayed the same day, and this occurred more often in the chronic kidney disease series. Only 51 persons in the healthy series had GFR determinations during the same time frame as the chronic kidney disease series. However, when indicator variables for these factors were considered in multivariable models, none of these factors changed the other coefficients substantively. There was less precision with the original MDRD equation applied to patients with chronic kidney disease for this study ($R^2 = 0.786$) compared with the MDRD study ($R^2 = 0.892$). The MDRD study had a larger sample size and used the average of 4 serum and 4 urine samples for measuring GFR with iothalamate clearance (25).

In summary, inaccurate estimates of GFR can occur if a serum creatinine–based equation is developed in a sample that is systematically different from the application population. This limits the generalizability of the abbreviated MDRD and Cockcroft–Gault equations, both developed in chronic kidney disease samples. The quadratic GFR equation is an improvement, but an equation developed from a general population sample is still needed. Future equations with alternative serum analytes, such as cystatin C (26), may ultimately be more accurate in predicting GFR across different populations.

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